

Appl. No. : 08/841,847
Filed : May 5, 1997

10 *26* *66* The microbubble preparation of claim *65* wherein said nonfluorocarbon modifier gas is selected from the group consisting of nitrogen, oxygen, carbon dioxide and mixtures thereof.

10 *27* *67* The microbubble preparation of claim *65* wherein said nonfluorocarbon modifier gas is air.

cont *4* *68* The microbubble preparation of claim *62*, wherein said gas osmotic agent has a water solubility of not more than about 0.5 mM at 25°C and one atmosphere.

B *5* *69* The microbubble preparation of claim *62* wherein the microbubble membrane comprises a surfactant.

6 *70* The microbubble preparation of claim *69* wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

7 *71* The microbubble preparation of claim *69* wherein said surfactant is a non-Newtonian surfactant.

8 *72* The microbubble preparation of claim *69* wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl starch, hydroxy ethyl starch fatty acid esters, dextrans, dextran fatty acid esters, sorbitol, sorbitol fatty acid esters, gelatin, serum albumins, phospholipids, polyoxyethylene fatty acids esters, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol

Appl. No. : 08/841,847
Filed : May 5, 1997

polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, cholesterol, oleic acid, sodium oleate and combinations thereof.

973. The microbubble preparation of claim ~~62~~¹ wherein the microbubble membrane comprises a liposome.

104. The microbubble preparation of claim ~~62~~¹ wherein the microbubble membrane comprises a proteinaceous material.

1178. The microbubble preparation of claim ~~14~~¹⁰ wherein said proteinaceous material is albumin.

1276. The microbubble preparation of claim ~~62~~¹ wherein said gas osmotic agent is perfluoropentane.

77. The microbubble preparation of claim 76 wherein said modifier gas is a fluorocarbon modifier gas.

78. The microbubble preparation of claim 76 wherein said modifier gas is a nonfluorocarbon modifier gas.

1378. The microbubble preparation of claim ~~78~~¹²⁷⁶ wherein said nonfluorocarbon modifier gas is selected from the group consisting of nitrogen, oxygen, carbon dioxide and mixtures thereof.

1480. The microbubble preparation of claim ~~78~~¹²⁷⁶ wherein said nonfluorocarbon modifier gas is air.

1581. The microbubble preparation of claim ~~78~~¹² wherein the microbubble membrane comprises a surfactant.

Appl. No. : 08/841,847
Filed : May 5, 1997

~~16~~ 82. The microbubble preparation of claim ~~81~~¹⁵ wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

~~17~~ 83. The microbubble preparation of claim ~~81~~¹⁵ wherein said surfactant is a fluorinated surfactant.

cont
B2
~~18~~ 84. The microbubble preparation of claim ~~76~~¹² wherein the microbubble membrane comprises a proteinaceous material.

~~20~~ 85. The microbubble preparation of claim ~~62~~¹ wherein said gas osmotic agent is perfluoropentane and said modifier gas is nitrogen.

L ~~20~~ 86. The microbubble preparation of claim ~~85~~¹⁹ wherein the microbubble membrane comprises a surfactant.

~~21~~ 87. The microbubble preparation of claim ~~85~~¹⁹ wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

~~22~~ 88. The microbubble preparation of claim ~~85~~¹⁹ wherein said surfactant is a non-Newtonian surfactant.

~~23~~ 89. The microbubble preparation of claim ~~85~~¹⁹ wherein said surfactant is a fluorinated surfactant.

~~24~~ 90. The microbubble preparation of claim ~~85~~¹⁹ wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester

Appl. No. : 08/841,847
Filed : May 5, 1997

salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl starch, hydroxy ethyl starch fatty acid esters, dextrans, dextran fatty acid esters, sorbitol, sorbitol fatty acid esters, gelatin, serum albumins, phospholipids, polyoxyethylene fatty acids esters, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, cholesterol oleic acid, sodium oleate and combinations thereof.

cont
B2
22
The microbubble preparation of claim 62 wherein said gas osmotic agent is perfluorohexane.

92. The microbubble preparation of claim 91 wherein said modifier gas is a fluorocarbon modifier gas.

93. The microbubble preparation of claim 91 wherein said modifier gas is a nonfluorocarbon modifier gas.

D 26
94. The microbubble preparation of claim 93 wherein said nonfluorocarbon modifier gas is selected from the group consisting of nitrogen, oxygen, carbon dioxide and mixtures thereof.

D 27
95. The microbubble preparation of claim 93 wherein said nonfluorocarbon modifier gas is air.

28
96. The microbubble preparation of claim 94 wherein the microbubble membrane comprises a surfactant.

Appl. No. : 08/841,847
Filed : May 5, 1997

²⁷ 97. The microbubble preparation of claim ²⁸ 96 wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

³⁰ 98. The microbubble preparation of claim ²⁸ 96 wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl starch, hydroxy ethyl starch fatty acid esters, dextrans, dextran fatty acid esters, sorbitol, sorbitol fatty acid esters, gelatin, serum albumins, phospholipids, polyoxyethylene fatty acids esters, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, cholesterol oleic acid, sodium oleate and combinations thereof.

³¹ 99. The microbubble preparation of claim ²⁸ 98 wherein said surfactant comprises a mixture of a phospholipid and a polyoxyethylene-polyoxypropylene copolymer.

³² 100. The microbubble preparation of claim ²⁵ 99 wherein the microbubble membrane comprises a proteinaceous material.

³³ 101. The microbubble preparation of claim ³² 100 wherein said proteinaceous material is albumin.

³⁴ 102. The microbubble preparation of claim 62 wherein said gas osmotic agent is perfluorohexane and said modifier gas is nitrogen.

Appl. No. : 08/841,847
Filed : May 5, 1997

³⁵
~~103~~. The microbubble preparation of claim ³⁴~~102~~ wherein the microbubble membrane comprises a surfactant.

³⁶
~~104~~. The microbubble preparation of claim ³⁵~~103~~ wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

Cont
B2
³⁷
~~105~~. The microbubble preparation of claim ³⁵~~103~~ wherein said surfactant is a non-Newtonian surfactant.

³⁸
~~106~~. The microbubble preparation of claim ³⁵~~103~~ wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl starch, hydroxy ethyl starch fatty acid esters, dextrans, dextran fatty acid esters, sorbitol, sorbitol fatty acid esters, gelatin, serum albumins, phospholipids, polyoxyethylene fatty acids esters, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, cholesterol, oleic acid, sodium oleate and combinations thereof.

³⁹
~~107~~. The microbubble preparation of claim ³⁵~~103~~ wherein said surfactant comprises a mixture of a phospholipid and a polyoxyethylene-polyoxypropylene copolymer.

⁴⁰
~~108~~. The microbubble preparation of claim ³⁹~~107~~ wherein said microbubble membrane further comprises a hydroxy ethel starch.

Appl. No. : 08/841,847
Filed : May 5, 1997

42 ~~109~~. A microbubble preparation comprising a aqueous medium having dispersed therein a plurality of osmotically stabilized microbubbles, said microbubbles comprising:

a generally spherical microbubble membrane containing at least one gas osmotic agent and at least one modifier gas wherein said gas osmotic agent comprises the vapor of a compound which is a liquid at 37°C and 760 Torr.

cont 42 ~~110~~. The microbubble preparation of claim ~~109~~ wherein said gas osmotic agent is selected from the group consisting of perfluorohexane, perfluorocyclohexane, perfluoroheptane, perfluorocycloheptane, perfluoromethylcyclohexane, perfluorodimethylcyclopentane, perfluorotrimethylcyclobutane, perfluorotriethylamine and combinations thereof.

43 ~~111~~. The microbubble preparation of claim ~~109~~ wherein said modifier gas is a fluorocarbon gas.

44 ~~112~~. The microbubble preparation of claim ~~111~~ wherein said fluorocarbon modifier gas is selected from the group comprising perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoromethylcyclobutane, perfluoropentane and perfluorocyclopentane.

45 ~~113~~. The microbubble preparation of claim ~~109~~ wherein said modifier gas is a nonfluorocarbon gas.

46 ~~114~~. The microbubble preparation of claim ~~113~~ wherein said nonfluorocarbon modifier gas is selected from the group consisting of nitrogen, oxygen, carbon dioxide and mixtures thereof.

47 ~~115~~. The microbubble preparation of claim ~~113~~ wherein said nonfluorocarbon modifier gas is air.

Appl. No. : 08/841,847
Filed : May 5, 1997

~~45/10~~ 116. The microbubble preparation of claim ~~109~~ ⁴¹ wherein the microbubble membrane comprises a surfactant.

~~49/11~~ 117. The microbubble preparation of claim ~~116~~ ⁴⁸ wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

cont
B2 ~~52/11~~ 118. The microbubble preparation of claim ~~117~~ ⁴⁸ wherein said surfactant is a non-Newtonian surfactant.

~~51/11~~ 119. The microbubble preparation of claim ~~118~~ ⁴⁸ wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl starch, hydroxy ethyl starch fatty acid esters, dextrans, dextran fatty acid esters, sorbitol, sorbitol fatty acid esters, gelatin, serum albumins, phospholipids, polyoxyethylene fatty acids esters, polyoxyethylene fatty alcohol ethers, polyoxyethylated sorbitan fatty acid esters, glycerol polyethylene glycol oxystearate, glycerol polyethylene glycol ricinoleate, ethoxylated soybean sterols, ethoxylated castor oil, cholesterol, oleic acid, sodium oleate and combinations thereof.

~~52/11~~ 120. The microbubble preparation of claim ~~119~~ ⁴¹ wherein the microbubble membrane comprises a liposome.

~~53/11~~ 121. The microbubble preparation of claim ~~120~~ ⁴¹ wherein the microbubble membrane comprises a proteinaceous material.

Appl. No. : 08/841,847
Filed : May 5, 1997

~~51~~ 122. The microbubble preparation of claim 121 wherein said proteinaceous material is albumin.

~~53~~ 123. A microbubble preparation comprising a aqueous medium having dispersed therein a plurality of osmotically stabilized microbubbles, said microbubbles comprising:

a generally spherical microbubble membrane comprising proteinaceous material containing at least one gas osmotic agent and at least one modifier gas.

~~54~~ 124. The microbubble preparation of claim ~~123~~, wherein said gas osmotic agent has a water solubility of not more than about 0.5 mM at 25°C and one atmosphere.

~~57~~ 125. The microbubble preparation of claim ~~123~~ wherein said gas osmotic agent comprises a fluorocarbon.

~~58~~ 126. The microbubble preparation of claim ~~125~~ wherein said fluorocarbon gas osmotic agent is selected from the group consisting of perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoromethylcyclobutane, perfluoropentane, perfluorocyclopentane, perfluoromethylcyclopentane, perfluorodimethylcyclobutanes, perfluorohexane, perfluorocyclohexane, perfluoroheptane, perfluorocycloheptane, perfluoromethylcyclohexane, perfluorodimethylcyclopentane, perfluorotrimethylcyclobutane, perfluorotriethylamine and combinations thereof.

127. The microbubble preparation of claim 123 wherein said modifier gas is a nonfluorocarbon gas.

Appl. No. : 08/841,847
Filed : May 5, 1997

~~55~~
~~55~~
128. The microbubble preparation of claim 127 wherein said nonfluorocarbon modifier gas is selected from the group consisting of nitrogen, oxygen, carbon dioxide and mixtures thereof.

129. The microbubble preparation of claim 123 wherein said modifier gas is a fluorocarbon gas.

130. The microbubble preparation of claim 129 wherein said fluorocarbon modifier gas is selected from the group comprising perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoromethylcyclobutane, perfluoropentane and perfluorocyclopentane.

~~60~~ 131. The microbubble preparation of claim ~~123~~ wherein the microbubble membrane further comprises a surfactant.

~~60~~ 132. The microbubble preparation of claim ~~131~~ wherein said surfactant is selected from the group consisting of nonionic surfactants, neutral surfactants, anionic surfactants, neutral fluorinated surfactants, anionic fluorinated surfactants and combinations thereof.

~~60~~ 133. The microbubble preparation of claim ~~131~~ wherein said surfactant is a non-Newtonian surfactant.

~~60~~ 134. The microbubble preparation of claim ~~131~~ wherein said surfactant is a fluorinated surfactant.

~~60~~ 135. The microbubble preparation of claim ~~131~~ wherein said surfactant is selected from the group consisting of polyoxypropylene polyoxyethylene copolymers, sugar esters, fatty alcohols, aliphatic amine oxides, hyaluronic acid aliphatic esters, hyaluronic acid aliphatic ester salts, dodecyl poly(ethyleneoxy)ethanol, nonylphenoxy poly(ethyleneoxy)ethanol, hydroxy ethyl